REMARKS

Support for the Claim Amendments

Claim 18 is amended to recite a liquid formulation comprising 1) an aqueous solvent comprising at least 50% by weight of water, 2) dispersed or solubilized within the solvent, biocompatible, biodegradable, synthetic, water soluble and covalently reactive macromers polymerizable to form a tissue adhesive hydrogel degrading in a period of less than one month after application to the tissue, and 3) dispersed within the formulation, particles of an anti-arrhythmic agent in a dosage effective to lengthen atrial effective refractory period. Support for the amendments may be found in the specification at least at page 4 lines 10-29, more particularly lines 18-20, which describes liquid formulations of macromers as soluble or dispersible polymers within an aqueous solvent and also define aqueous solvent to be at least about 50% by weight of water; from page 17, starting at line 18 to page 18, line 9 which describes the dispersion of anti-arrhythmic drugs within macromer formulation; from page 18, line 10 to page 19, line 15, which describes the formation of particles from water-soluble drugs.

Claim 21 is amended to define the particles as comprising the anti-arrhythmic agent. Support for this amendment may be found at least from page 18, line 10 to page 19, line 15, which describes the formation of particles from water-soluble drugs.

Applicant thus submits that these amendments do not introduce new matter. Accordingly, Applicant respectfully requests that these amendments be entered.

Rejection of claims under 32 USC §103(a)

1. Claims 18-26 were rejected under 35 USC §103(c) as being unpatentable over Sawhney et al. (US5900245) in view of Levy et al. (US5387419). Applicant hereby amends the claims to more clearly point out that the claimed compositions are liquid formulations of aqueous nature with macromers dispersed or solubilized therein and also dispersed therein particles of an anti-arrhythmic agent. Applicant respectfully submits that the present claims are patentable over the

previously cited art as the references lack the required incentive for the cited combination and when combined the references do not teach the invention as a whole.

Specifically, while Sawhney teaches the general delivery of drugs from its hydrogels, it does not teach or suggest compositions for the delivery of drugs to treat arrhythmia or compositions for the delivery of drugs in particulate form from aqueous formulations that forms hydrogels, such as poorly water-soluble drugs or drugs formulated to form particles in an aqueous solvent. Further, Sawhney, alone, does not render the present invention obvious as a skilled artisan reading Sawhney would not derive how well drugs in particulate form could diffuse out of a hydrogel network in a controlled manner, nor how, if any, the mechanical properties of the hydrogel, such as compliance or adherence, would be affected by the presence of the particles within the gel. Thus one reading Sawhney alone would not be motivated to prepare the aqueous compositions of the invention which are precursor formulations for the formation of hydrogels for the delivery of drugs.

The inventors of the presently claimed invention have recognized that one of the deficiencies with the compositions taught by Sawhney is that these hydrogels provide poor control over the delivery of water-soluble drugs over periods of time extending beyond a few hours. The present inventors have realized that to provide control over the delivery of drugs contained within the hydrogels to the aqueous environment of a living body, they must rely on the poor water solubility of the drug to delay its diffusion to the tissue adjacent the implanted hydrogel. Sawhney did not appreciate, teach or suggest that drug particles, such as poor water-soluble drugs or coated drugs, could be efficiently delivered exclusively to neighboring tissue over an extended period of time of several days.

A skilled artisan trying to improve upon the deficiencies of Sawhney's hydrogels would not look to the teachings of Levy as Levy effects control of the delivery of the drug by relying on the hydrophobic nature of the polymeric matrices to slow the diffusion of the drug into the tissue and the absorption of the aqueous body fluid within the matrices. Indeed, while Levy teaches compositions for the treatment of arrhythmia, Levy nonetheless fails to cure all the deficiencies of Sawhney in that it also does not teach or suggest compositions for the delivery of drug

particles from aqueous formulations that form hydrogels. The polymeric matrices taught in Levy are either 1) hydrophobic matrices (see col. 3, lines 18-33; col.5, line 56 to col. 6 line10) or 2) in the case of collagen (col. 3, line 32; col. 6, line 9), not covalently reactive macromer polymerizable to form a tissue adhesive hydrogel; they do not contain water-soluble macromers capable of crosslinking to form hydrogels. The processes taught in Levy do not concern the suspension of particles in aqueous formulations. They mostly concern the formation of blends between hydrophobic polymers and the drug either in neat form or optionally with the assistance of an organic solvent in which both the drug and the polymer are soluble (see col. 3 line 47-60; col. 7, line 53 to col. 8 line 8). Levy formulations with an organic solvent are clearly not intended for direct implantation within the body as these formulations are either not biocompatible (see examples 3, 8, 9, and 10 (dimethylacetamide), example 4 (chloroform, methylene chloride and ethylacetate), and example 11 (methylene chloride and acetic acid)), or further taught to be cast into films or molded into substrate shape (see col. 4, lines 1-8; and examples 1, 2, 3, 8, 10, 11). Levy constantly refers to these compositions as either films or substrates indicative that these matrices are not in the form of aqueous solutions nor hydrogels.

Accordingly, the cited references are not combinable as neither Sawhney, nor Levy teaches or suggests modification to their compositions to arrive at the presently claimed compositions. Rather, Levy teaches away from the present compositions as Levy teaches compositions in which the release of the drug from the matrix within the aqueous environment of the body is controlled by the hydrophobicity of the matrix preferably for the delivery of *water soluble drugs* (see col. 6, line 67 to col. 7, line 2), or of poorly water-soluble drugs solubilized in hydrophobic matrices (see example 8, where amiodarone is solubilized in polar organic solvent and mixed into a polyurethane matrix in a soluble form then cast) - not in particulate form within water-soluble macromers that can form a hydrophilic matrix.

Even if combined the cited references do not teach the claimed invention as a whole as neither references teaches nor suggests the use of an anti-arrhythmic drug in a particulate form within an aqueous formulation of a covalently reactive hydrophilic macromer which is capable of polymerizing to form a tissue adhesive hydrogel. Accordingly, Applicant respectfully submit

that the present claims 18 to 26 are patentable over the previously cited references, and kindly requests that the rejection be reconsidered in view of the present amendment and withdrawn.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement along with the list of cited references (Form 1449) and copies thereof (see Appendix) are being filed with the filing of a RCE under 37 CFR §1.97(b)(4). Applicant kindly requests consideration of these references and return of the Form 1449 bearing the Examiner's initials.